Best Practice

TOPIC IN REVIEW

Plant sterol and stanol margarines and health

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A new polyunsaturated margarine with added plant stanols, Benecol, has been introduced in the United States and in several European countries, and a similar margarine (Take Control) with added plant sterols is available in the United States and will be introduced in Europe under the Flora label later this year. These products lower serum concentrations of cholesterol, but they are expensive.[1-14] In the United States, the cost is about $4.00 for a 250-g tub. This article considers quantitatively the health aspects of adding plant sterols and stanols to margarines and other foods.

Summary points

- Plant sterols and stanols reduce the absorption of cholesterol from the gut and so lower serum concentrations of cholesterol
- Plant sterols or stanols that have been esterified to increase their lipid solubility can be incorporated into margarines and other foods
- The 2 g of plant sterol or stanol added to a 25-g daily portion of margarine reduces serum concentrations of low-density-lipoprotein cholesterol by an average of 0.54 mmol/L (21 mg/dL) in people aged 50 to 59, 0.43 mmol/L (17 mg/dL) in those aged 40 to 49, and 0.33 mmol/L (13 mg/dL) in those aged 30 to 39
- A reduction in the risk of heart disease of about 25% would be expected for this reduction in low-density-lipoprotein cholesterol; this is larger than the effect that could be expected to be achieved by people reducing their intake of saturated fat
- The added costs of $120 per person per year will limit consumption; however, if stanols and sterols become cheaper, their introduction into the food chain will make them an important innovation in the primary prevention of heart disease

METHODS

Randomized trials included in this review were identified by a MEDLINE search using the term "plant sterols." Additional trials were identified from citations in these articles and in review articles. Other trials in children with familial hypercholesterolemia were not included.

PLANT STEROLS AND STANOLS

Sterols are an essential component of cell membranes, and both animals and plants produce them. The sterol ring is common to all sterols; the differences are in the side chain. Cholesterol is exclusively an animal sterol. More than 40 plant sterols (or phytosterols) have been identified, but β-sitosterol (especially), campesterol, and stigmasterol are the most abundant. These 3 sterols are structurally similar to cholesterol: they are all 4-desmethyl sterols (containing no methyl groups at carbon atom 4).

Stanols are saturated sterols (they have no double bonds in the sterol ring). Stanols are less abundant in nature than sterols. Plant stanols are produced by hydrogenating sterols. The term "sterol" is sometimes used as a generic term to include unsaturated sterols and saturated stanols, but it is used here to refer specifically to the unsaturated compounds.

It was recognized in the 1950s that plant sterols lower serum concentrations of cholesterol[15]; they do this by reducing the absorption of cholesterol from the gut by competing for the limited space for cholesterol in mixed micelles (the "packages" in the intestinal lumen that deliver mixtures of lipids for absorption into the mucosal cells).[6,11,16-18] The average consumption of spreads (margarine and butter) is 20 to 25 g per person per day in Europe but a little lower in the United States (15-10 g per person per day). The estimates of effect apply to an average consumption of 25 g per day (an 8-z tub lasting 10 days for 1 person). The fortified margarines contain 2 g of plant sterols or stanols per daily portion. About 0.25 g of plant sterols and 0.3 g of cholesterol occur naturally in the daily diet; the amount of plant sterols consumed daily is twice as much in a vegetarian diet. The added plant sterols or stanols in fortified margarine reduce the absorption of cholesterol in the gut—both dietary and endogenous (that is, excreted in bile)—by about half, from the normal proportion of about half the total cholesterol to one quarter. This reduced absorption lowers serum cholesterol concentrations despite the compensatory increase in cholesterol synthesis that occurs in the liver and other tissues.[6,11] Plant sterols are potentially atherogenic like cholesterol,[19] but atherogenesis does not occur because so little of the plant sterols is absorbed (for example, about 5% of β-sitosterol, 15% of campesterol, and less than 1% of dietary stanols are absorbed).[16]

The use of plant sterols as cholesterol-lowering drugs has been limited: initially the market was small, and later the greater efficacy of the statins was evident. By the 1980s, however, it was recognized that as naturally occurring substances, plant sterols and stanols could be added to foods. Because fats are needed to solubilize sterols, margarines are an ideal vehicle for them, although cream cheese, salad dressing, and yogurt are also used. Esterifi-

cation of the plant sterols and stanols with long-chain fatty acids increases their lipid solubility and facilitates their incorporation into these foods. Benecol was the first fortified margarine, and stanols were added because the evidence suggested that they had greater potential to lower cholesterol than sterols, and the amount absorbed from the gut is negligible.[16,18,20,21]

BENEFITS OF PLANT STEROLS AND STANOLS

The table summarizes the results of randomized double-blind trials in adults that compared the ability of polyunsaturated margarines with and without added plant sterols to lower cholesterol concentrations. The effect of electing trial subjects who had high concentrations of serum cholesterol in some trials was modest, and with the exception of 1 small trial,[13] mean serum concentrations of low-density-lipoprotein (LDL) cholesterol in the control groups ranged from 3.0 to 4.5 mmol/L (116-174 mg/dL) (median, 3.8 mmol/L [147 mg/dL]), close to the age-specific mean found in the western world. The randomized comparisons in 2 trials suggested that there was little difference in the extent to which sterols or stanols lower cholesterol concentrations (although the confidence intervals are consistent with the evidence above that stanols are better).[1,12] The table shows the reduction in LDL cholesterol in each trial; the reductions in total cholesterol concentrations were similar, and there was little change in serum concentrations of high-density-lipoprotein cholesterol or triglyceride.

The figure shows the reduction in concentrations of LDL cholesterol achieved in each trial and the dose of plant sterol or stanol. The reduction in the concentration of LDL cholesterol at each dose significantly increases with age. In each age group, the dose-response relation is continuous up to a dose of about 2 g of plant sterol or stanol per day. At higher doses, no further reduction in concentrations of LDL cholesterol is apparent, confirming the evidence of a plateau identified by earlier nonrandomized studies.[17] At doses of 2 g per day and higher, the average reduction in serum LDL cholesterol concentrations was 0.54 mmol/L (21 mg/dL) (14%; 95% confidence interval, 0.46-0.63 mmol/L) for participants aged 50 to 59,[3,6,8,11] 0.43 mmol/L (17 mg/dL) (9%; 0.37-0.47 mmol/L) in participants aged 40 to 49,[1,4,5,13] and 0.33 mmol/L (13 mg/dL) (11%; 0.25-0.40 mmol/L) for those aged 30 to 39[1,2,5,10]; this trend was statistically significant ($P = 0.005$). At a dose of 2 g per day (the amount added to a 25-g daily portion of fortified margarine), the reduction in LDL-cholesterol concentration is likely to be at least 0.5 mmol/L (20 mg/dL) for those aged 50 to 59 and 0.4 mmol/L (15 mg/dL) for those aged 40 to 49.

Data from observational studies and randomized trials indicate that in people aged 50 to 59, the reduction in LDL-cholesterol concentration of about 0.5 mmol/L would reduce the risk of heart disease by about 25% after about 2 years.[22] In younger people, the proportionate reduction in risk would be similar (the reduction in cholesterol concentrations is smaller, but the association between cholesterol and heart disease is stronger).[22] Trials of 6 different interventions to lower serum cholesterol concentrations have all found a reduction in the incidence of heart disease (these interventions include 4 pharmacologically unrelated drugs, a reduction in dietary saturated fat, and ileal bypass surgery).[22,23] Nothing except a reduction in cholesterol concentration is common to the 6 interventions, and for each intervention, the proportionate reduction in mortality from heart disease is commensurate with the reduction in cholesterol concentration.[17,18] Margarines with plant sterols or stanols thus reduce the risk of heart disease by one quarter: this is the reduction expected from the decrease in serum cholesterol.

This is an impressive result for a dietary change that, price apart, is modest. It is larger than the effect that could be expected if people ate less animal fat. For a person replacing butter with a plant sterol margarine, the reduction in cholesterol concentration would be even greater. Replacing butter with ordinary polyunsaturated margarines lowers total serum and LDL-cholesterol concentrations by about 0.3 mmol/L (12 mg/dL),[24,25] so the overall reduction would be about 0.7 mmol/L (27 mg/dL), or as much as any cholesterol-lowering drug except statins.

EFFICACY IN COMBINATION WITH LOW-FAT DIETS

One nonrandomized study found only a small average reduction in LDL-cholesterol concentrations (0.16 mmol/L [6 mg/dL]) despite that participants took 3 g of plant stanols daily.[26] The participants were on a low-fat and low-cholesterol diet, and the result was interpreted as suggesting that plant sterols were ineffective when dietary fat, dietary cholesterol, or LDL-cholesterol concentrations are low. This is unlikely. In 2 recent randomized trials of stanol margarines in which participants were on low-fat, low-cholesterol diets, the reductions in serum concentrations of LDL cholesterol were similar to those found in other trials in which the intake of dietary fat was higher.[4,9] Plant stanols were equally effective in patients taking statins, who had mean LDL-cholesterol concentrations of only 2.9 mmol/L (112 mg/dL).[6] Other explanations for the discrepancy are more plausible: chance (at the upper confidence interval of the result, an LDL-cholesterol reduction of 0.43 mmol/L is what might be expected) or the fact that the stanol was administered in capsules and not esterified and blended into the fat of a meal. (Sterols administered in capsules may not disperse fully or dissolve in the gut, limiting their ability to reduce the absorption of cholesterol.[9])

Table 1 *Randomized double-blind trials that reported the difference in serum cholesterol concentrations obtained from using polyunsaturated margarines with and without added plant sterols or stanols. Trials were parallel group trials, unless indicated otherwise*

Trial	No. of participants in treatment group/placebo group	Mean age, yr	Duration of trial, wk	Type	Average daily dose, g	Placebo-adjusted reduction in serum LDL cholesterol, mmol/L (95% CI)
Westrate and Meijer[1] (Netherlands)	80*	45	3.5	Stanol	2.7	0.42 (0.33–0.51)
				Sterol	3.2	0.44 (0.35–0.53)
Hendriks et al[2] (Netherlands)	80*	37	3.5	Sterol	0.8	0.20 (0.10–0.31)
				Sterol	1.6	0.26 (0.15–0.36)
				Sterol	3.2	0.30 (0.20–0.41)
Miettinen et al[3] (Helsinki)	51/51	50	52	Stanol	1.8	0.41 (0.29–0.53)
	51/51			Stanol	2.6	0.59 (0.47–0.71)
Hallikainen and Uusitupa[4] (Finland)	38/17	43	8	Stanol	2.3	0.47 (0.24–0.70)
Vanhanen et al[5] (Helsinki)	34/33	46	6	Stanol	3.4†	0.33 (0.15–0.51)
Gylling et al[6] (Helsinki)	22*	51	7	Stanol	3.0	0.53 (0.30–0.76)
Jones et al[7] (Montreal)	22*	35	1.4	Sterol	1.7‡	0.30 (0.21–0.39)
Gylling and Miettinen[8] (Helsinki)	21*	53	5	Stanol	2.4§	0.45 (0.24–0.66)
Jones et al[9] (Montreal)	16/16	about 50	4	Stanol	1.9	0.64 (0.06–1.22)
Niinikoski et al[10] (Finland)	12/12	37	5	Stanol	3.0	0.50 (0.06–0.94)
Gylling and Miettinen[11] (Helsinki)	11*	58	6	Stanol	3.0	0.50 (0.29–0.71)
Miettinen and Vanhanen[12] (Helsinki)	9/8	45	9	Stanol	1.0†	0.28 (0.01–0.55)¶
	7/8			Sterol	0.8†	0.26 (−0.05–0.57)¶
Vanhanen et al[13] (Helsinki)	7/8	47	6	Stanol	0.8†	0.28 (0.0–0.56)¶
				Stanol	2.0†	0.54 (0.23–0.85)
Plat and Mensink[14] (Netherlands)	70/42	33	8	Stanol	4.0	0.36 (0.23–0.49)

LDL = low-density-lipoprotein; CI = confidence interval
*Crossover trial.
†In mayonnaise.
‡In olive oil.
§In butter.
¶Data from these small trials, which tested low doses, are combined in the figure.

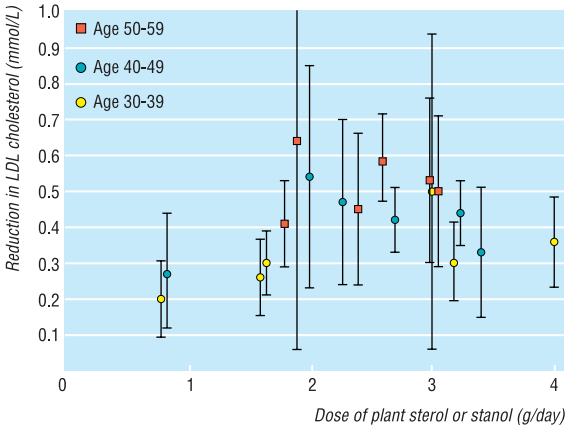
SAFETY

The most important concern about plant sterols is that they reduce the absorption of some fat-soluble vitamins. Randomized trials have shown that plant sterols and stanols lower blood concentrations of β-carotene by about 25%, concentrations of α-carotene by 10%, and concentrations of vitamin E by 8%.[1,2,8,27] Because these vitamins protect LDL cholesterol from oxidation, and sterols and stanols reduce the amount of LDL cholesterol to be protected, the changes in blood concentrations of the vitamins were adjusted in the trials for the lower concentrations of LDL cholesterol. With this adjustment, concentrations of vitamin E were not lower, but concentrations of β carotene were reduced by between 8% and 19%.[1,2,8,27] Randomized trials showed no benefit in increasing the blood concentrations of β-carotene and vitamin E by greater proportions than these,[28,29] although we do not know whether this is the case for other carotenes. Eating more fruit and vegetables would counter the decrease in absorption. The blood concentration of vitamin D is unaffected.[2,8] No other side effects or biochemical anomalies were evident in the randomized trials of plant sterol or stanol margarines (1 of which lasted a year[3]), in earlier studies testing doses as high as 3 g per day for 3 years, or in animal studies testing proportionately higher doses.[16,17,30] Stanol margarines have been sold in Finland for 3 years without evidence of hazard, and a tenth of the amount of plant sterols found in these margarines occurs naturally in a normal diet. Plant sterols or stanols do not adversely affect the taste or consistency of margarines.[3,10]

THE PLACE OF STEROL AND STANOL MARGARINES IN THE DIET

The excess cost per person of margarines containing added plant sterols or stanols is about 33 cents per day, or $120 per year. Affluent people may willingly pay this to reduce their risk of death from heart disease by a quarter, but poorer people, who are at higher risk of heart disease, will tend to be dissuaded from buying the product. The cost reflects the large amount of raw material needed (about 2,500 parts to extract 1 part of sterol). Moreover, supplies are limited. The present sources—a byproduct in the refining of vegetable oils or the oil obtained from pinewood pulp in papermaking—can supply only about 10% of the people in developed countries. In the foreseeable future, the product will be used only by a minority of people. However, in many countries, there is also a legal obstacle: no health claim can be made in the advertising of these margarines because they are a food, not a drug. More people might buy the product if they were aware of the size of the health benefit.

Plant sterol and stanol margarines may appeal to patients with ischemic heart disease, but they should not replace statins because the reduction in the concentration of LDL cholesterol is greater with statins. Both could be taken together, however, because the cholesterol-lowering effects of the 2 are additive.[6] The overall costs of the 2 are equivalent: statins cost about 3 times as much as plant sterol margarines, but they lower serum cholesterol by 3 times as much.



Results of randomized double-blind trials of margarines with and without added plant sterols or stanols showing the reduction in serum concentrations of low-density-lipoprotein (LDL) cholesterol (95% confidence intervals) plotted against the daily dose. The data are from the table.

In the longer term, the addition of plant sterols and stanols to foods could be an important public health policy if new technology and economies of scale can lower the cost and enable a greater demand to be met. The serum cholesterol concentration of the average older adult in western countries is high (5.7-6.0 mmol/L [220-240 mg/dL]), with a correspondingly high lifetime risk of death from heart disease (about 25%). Introducing plant sterols into the food chain would lower the average serum cholesterol concentration in western countries, with the added advantage of "demedicalizing" the reduction (that is, one would not have to become a patient to benefit). There is a precedent for such fortification: in the United States, folic acid has been added to flour since 1997. In addition to the expected reduction in the incidence of neural tube defects, there has also been a significant reduction in the average serum concentration of homocysteine,[31] which is likely to reduce mortality from heart disease.

The launch of margarines containing plant sterols and stanols is a welcome first step in what may become an important innovation in the primary prevention of ischemic heart disease. It is to be hoped that in the longer term, plant sterols and stanols will become cheap and plentiful so that they can be added to foods eaten by most of the population.

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capsule

Drug resistant bacteria cause fresh concern Infections caused by so-called "superbugs," resistant to most available antibiotics, are causing renewed concerns worldwide. Four recent outbreaks of new and more virulent strains of disease caused by contact with animals or contaminated food were reported in the *New England Journal of Medicine* (*N Engl J Med* 2000;342:1280-1281).

capsule

Moderate drinking protects against diabetes US doctors who drink up to 1 unit of alcohol a day could be protecting themselves from type 2 diabetes (*Arch Intern Med* 2000;160:1025-1030). Data from the Physicians Health Study, a cohort of over 20,000 male doctors, shows a clear dose-response relation between alcohol intake of up to 1 drink a day and reduced risk. Note, though, that there weren't enough heavy drinkers in the cohort to study the association beyond moderate drinking.